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DIALOG(R)File 20:Dialog Global Reporter

08613830 (THIS IS THE FULLTEXT)
New Report Assesses the Impact of Pharmacogenomics on Pharmaceutical R&D
BUSINESS WIRE
December 08, 1999
JOURNAL CODE: WBWE LANGUAGE: English RECORD TYPE: FULLTEXT
WORD COUNT: 576

WOBURN, Mass.--(BW HealthWire)--Dec. 8, 1999--AdvanceTech Monitor announces the publication of an industry report on the "The Impact of Pharmacogenomics on Drug Discovery and Development". The report examines the drivers behind the emergence of this field, reviews the major industry players and their technologies, and discusses the attractions and barriers to the application of pharmacogenomic technologies in pharmaceutical R&D.

Some of the major findings of this report include the following:

--The pharmaceutical industry still struggles with the integration of the more established genomic technologies and some companies therefore are reluctant to adopt the latest concepts in pharmacogenomics, despite its promise of safer and more effective drugs;

--Biotech companies focus more on functional genomics and proteomics than on pharmacogenomics because of its requirement for massive and expensive studies;

--Gene-disease and gene-metabolism association studies are difficult to interpret due to inherent redundancies in biochemical pathways and complex interactions between genetic and environmental factors;

--Linkage disequilibrium studies using smaller and more manageable study populations may be the key to the discovery of gene-disease associations in complex diseases, despite the requirement of densely populated genetic maps;

--In order to carry out large-scale genotyping studies (with 20 million genotypes) at a target cost of $200,000 per study, the cost of a single SNP assay needs to be reduced to one cent per genotype - or by one to two orders of magnitude from the current pricing structure;

--Primer extension, cleavage, heteroduplex and ligation-based genotyping assays have the ability to score single or small groups of SNPs, but primer extension methods may likely play a key role in SNP detection; other scalable detection systems include virtual microarrays and PCR independent SNP assays;

--The formation of the SNP consortium was one response to considerable concerns in the industry and public regarding patenting of key genetic markers by pharmaco-genomic companies;

--The FDA currently views pharmacogenomics as one source of data in support of a drug's safety and efficacy that may but does not have to be submitted to obtain regulatory approval of a new drug;

--Over the next five years, the size of the diagnostics market, currently the smallest segment of the pharmacogenomics market, will surpass the heretofore largest segment of gene-disease association studies; the clinical trial market will remain a small segment of the total market for pharmacogenomics;

--A significant medical benefit derived from a pharmacogenomics-based drug can add $500 million in incremental revenues per year for such a drug;

--Although "home-brew" genetic tests are currently overseen by CLIA regulations of laboratory practice that set lower standards than FDA oversight, the FDA will be forced to require FDA approval for genetic test kits along with adherence to GMP regulations.

The report has been published in November, 1999 and is available as a printed hardcopy and a searchable CD-ROM.

AdvanceTech Monitor is a Boston-based technology and business publication company that specializes in the pharmaceutical and energy

industries.

A complete Table of Contents and a twenty page-long executive summary of the report is displayed at the publisher's website. For more information, contact Dr. Mike Silver at 781-939-2585 or m.silver@advancetechmonitor.com or visit our website at http://www.advancetechmonitor.com

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07:03 EST DECEMBER 8, 1999

DESCRIPTORS: Research & Development; Company News
PROVINCE/STATE: Massachusetts
SIC CODES/DESCRIPTIONS: 2834 (Pharmaceutical Preparations)
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Pharmacogenomics - Impact on Drug Discovery

Advances Toward the Development of Highly Targeted, More Effective and Safer Disease Treatments

Background

Starting in 1997, triggered in part by the Abbott-Genset alliance, pharmacogenomics began to emerge as a serious discipline in pharmaceutical R&D. The industry's interes in pharmacogenomics with its promise of the right drug for the right person at the right time is rapidly increasing. Major drivers behind the application of pharmacogenomics are the needs for:

1. faster innovation (to make up for an estimated innovation deficit of 1.3 NCEs in 1999 among the top 10 pharmaceutical companies).
2. lowering R&D costs (costs in research-focused companies increased from 11-12% of sales in the 1970's to 19-21% in the 1990's).
3. reducing adverse drug reactions (ADR), which are increasingly recognized as a serious medical problem (ADR causes more than 100,000 deaths annually).

Pulled along by the Human Genome Project and its commercial counterparts, pharmacogenomics is giving birth to a host of technology platform companies with product offerings ranging from powerful methods to detect genetic polymorphisms to new approaches for the identification of genes critical to complex, high-incidence diseases through tests to qualify users of a particular drug. Massive genotyping experiments promise to generate new, higher quality targets for drug discovery and novel diagnostic assays to target drugs to an individual's genetic predisposition.The opportunities are enormous, and so are the challenges.

- How can big pharma thrive in an atmosphere of micro-segmented markets?
- Will available technologies permit cost-effective massive genotyping?
- Should pharmacogenomic capabilities be built in-house or outsourced?
- Will the healthcare system risk high drug prices for the promise of lower overa healthcare costs?
- Will the benefit of pharmacogenomics-era drugs outweigh the costs?
- How will the public react to the threat of invasion of genetic privacy and its attendant consequences?

This industry report provides answers to these questions while covering:

- Creation of pharmacogenomic opportunities through emerging technologies
- Strategies of big pharma and biotech platform companies to seize pharmacogenomic opportunities
- Realities of developing pharmacogenomics-based drugs for complex, high-incidence diseases
- Impacts of pharmacogenomics on revenue and profitability
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Pharmacogenomics - Impact on Drug Discovery

Executive Summary

1.1 Origins and Evolution of Pharmacogenomics

Pharmaceutical companies, perceiving an "innovation deficit," are working to increase their output of new drugs. These drugs will enter a market environment in which healthcare companies and their regulators work to contain ever-rising costs. Cost containment efforts are mitigated, however, by an increasingly well-informed public, itself the subject of direct-to-consumer pharmaceutical marketing efforts. This combination of forces demands that providers of products for healthcare pay increased attention to cost-benefit performance.

Rapid advances in genomics have touched off a commercial race to identify new gene targets, which become subjects of big pharma's "industrialized" drug discovery assembly lines in a race to alleviate the innovation deficit. The story does not end there, because genomic advances have reignited interest in genetic variability and its application to the study of drug response variations among individuals. It is hoped that such studies can provide new drugs and diagnostics that can enhance safety and efficacy, while reducing the costs accompanying inappropriate drug therapy and adverse drug reactions.

The emerging field of pharmacogenomics promises to satisfy these requirements, perhaps at the cost of reducing the size of the market for resulting drugs. The industry hopes that the benefits of resultant radically improved drugs can more than offset potential losses from the elimination of poor responder populations.

This report examines the origins, development, and prospects for pharmacogenomics.

- The opening chapter describes the emerging new paradigm in drug discovery, traces the rise of genomics and its impacts on drug discovery, examines the emergence of genomics as a commercial enterprise, and finally describes in depth the emergence and basic concepts of pharmacogenomics.
- The second chapter deals with the principles and significance of the varied and complex group of technologies underlying pharmacogenomics.
- A third chapter provides a view of pharmacogenomics from the market perspective. Here the report examines in depth the economic issues underlying the need for pharmacogenomics, the business strategies of both technology suppliers and pharmaceutical companies in addressing these issues, and the competitive environment. The chapter continues with an attempt to estimate current and future revenues from the provision of products and services for pharmacogenomics and revenue impacts on big pharma from pharmacogenomics. The market analysis chapter ends with an examination of future trends in pharmacogenomics and an attempt to answer the fundamental question: pharmacogenomics – revolution or evolution?
- A fourth chapter provides an overview of the companies involved in pharmacogenomics.
- The final chapter presents two case studies of two leading genomics companies: Millennium Pharmaceuticals and Incyte Pharmaceuticals.

Big Pharma, Big Problems

Sales for research-intensive pharmaceutical companies increased by approximately 13% for 1998 and 1999, while R&D expenditure increases for those years were comparable at 11% and 14%, respectively. The perceived innovation deficit is perhaps better reflected by the fact that R&D expenditures as a percentage of sales rose from 11-12% in the 1970s to 19-21% in the 1994-1999 period. Jurgen Drews calculated in 1996 that big pharma would by extrapolation suffer a deficit of 1.3 NCEs (new chemical entities) per year per company from the number needed to maintain a 10% growth rate. Several large pharmaceutical companies have announced goals of at least 3 NCEs per year, but actual figures are still at less than 1.

A revolution in the way new drugs are discovered and developed appears necessary for the continued health of the industry. Areas needing improvement include the time and costs required for drug discovery and development. Significant improvements in both times and costs might be possible with higher quality drug targets, the ability to eliminate compounds at earlier stages in the overall process, and improvements in the selection of clinical trial populations. Each of these factors is addressable by pharmacogenomics.

New Directions for Biotechnology

Funding problems have driven some biotechnology companies to shift their focus from the discovery and development of therapeutic agents to the provision of pharmacogenomic information and services. Variagenics and Lynx Therapeutics are two examples of the trend. Aside from these, a new category of company has emerged recently to build databases of medical information coupled with genotype data from individuals with specific diseases. These companies have or seek pharmacogenomic collaborations with big pharma. In a third category, genomics companies are adding pharmacogenomic information to their databases and collaborate with pharmaceutical companies on both new and existing drugs. While considerable pharmacogenomic activity is underway, its value to big pharma remains largely hypothetical, a fact that has limited the number and scope of deals.

Problems on the Demand Side

The push by big pharma to produce more drugs faster is countered by increasing awareness of deficits in the safety and efficacy of existing drugs, which are judged on statistical criteria derived from heterogeneous populations. Most drugs are effective for only a subset of individuals with a given diagnosis. Drug response differences among individuals are determined in significant measure by genetic variation. Thus pharmacogenomics promises to get the right drug to the right patient at the right time.

The Emerging New Paradigm in Drug Discovery

In its efforts to make crucial improvements in R&D productivity, the pharmaceutical industry is in the process of adopting two related perspectives – 1) the industrialization of drug discovery and development and 2) the application of genomics and genetics to drug discovery and development. Two case studies that illustrate these aspects of genomics are presented for two leading genomics companies, Incyte Pharmaceuticals and Millennium Pharmaceuticals.

Drug discovery began as a predominantly empirical science from which a large body of heuristic knowledge emerged. Advances in molecular biology and related sciences led to the identification of molecular targets and increasingly rational approaches to drug discovery. Advances in combinatorial chemistry produced a plethora of compounds to test with the growing collection of targets, leading to what has been termed the "industrialization" of drug discovery.

Yet such industrialization really needs to provide more than just vast acceleration to an imperfect, less-than-fully-rational process. The drive towards rationality, coupled with the rise of genomics, the emergence of effective knowledge management systems and the need to improve R&D cost-efficiency, leads inevitably towards the adoption of gene-based technologies, discoveries, and perspectives.

The ability of genomics to discover new drug targets is tempered by the realization that genetically complex, high-incidence diseases may involve defects in several

genes acting in concert with environmental factors to produce disease. Thus new methods – those of pharmacogenomics – may be required to generate the radically new approaches required to produce improved drugs for these conditions. A new paradigm is evolving based on the intersection of emerging new technologies, shifting market realities, and evolving pharmaceutical industry economics. Pharmaceutical companies are staking claims to the new territory. Scientists believe that a Mother Lode of pharmacogenomic-based treasure may well exist, waiting only to be discovered.

Early indications are favorable, but nothing really dramatic has yet been accomplished to prove the existence of such a treasure trove. As will be seen, the enterprise rests in large measure on a fundamental genetic hypothesis that has yet to be verified. A major part of the effort being expended by small, medium, and large-sized companies is being directed toward the testing of this hypothesis.

The remainder of this report is designed:

- To provide an in-depth view of current knowledge about pharmacogenomics;
- To provide some sense of where the field may be heading;
- To assess the impacts pharmacogenomics might have on big pharma in particular and the healthcare delivery system in general.

Genomics Has Expanded to Embrace Genetic Variation

Studies of genetic variation promise to provide an important route to the identification of genes that play a key role in the common diseases – e.g., coronary disease, hypertension, obesity, schizo-phrenia, Alzheimer's disease – that constitute primary market targets for big pharma. Geneticists have long been preoccupied with studying simple single-gene diseases using familial linkage methods. Complex, high-incidence, multi-gene diseases are thought to require a different approach, for which SNPs (single nucleotide polymorphisms) can play a key role in holding the size of required genetic studies down to manageable levels.

Several million SNPs exist in the human genome, and the largest SNP maps generated to date contain about 60,000 of them. Efforts, both public and private to generate much denser SNP maps are ongoing. The maps can be used in genome-wide studies of cases and controls designed to identify markers found only in one of those two groups. These markers, in turn, provide valuable clues to the location and identity of complex disease genes.

The Emergence of Commercial Genotyping

As the needs for genotyping grew, new companies and technologies emerged to fill the gap. Genomics companies turned their attention to discovering and mapping SNPs, population genetic companies began tapping into public medical databases for phenotype information to be combined with new genotype data, and "genomic tool" companies devised new and improved technologies for high throughput automated genotyping.

Eurona Medical, with access to Swedish public health information, played a pioneering role in population genetics, followed later by Gemini Research and Oxagen in the U.K., deCODE Genetics in Iceland, and Variagenics and Genaissance in the U.S. Affymetrix's GeneChip® microarrays have been adapted to genome-wide screening of up to 1,500 SNPs per specimen. Other companies – e.g., Perkin-Elmer, Orchid Biocomputer, Third Wave Technologies, and Seque-nom – are deploying diverse technologies for detecting smaller numbers of SNPs in larger numbers of specimens.

The Emergence of Pharmacogenomics

Pharmacogenomics – the application of genomic methods and perspectives to the study of drug response genes – has its origins in pharmacogenetics, which emerged during the late 1950s with the postulate that adverse drug reactions might be traced to genetic differences affecting the activity of enzymes involved in drug metabolism. Studies confirmed this hypothesis and led to the discovery of more than 100 examples of abnormal drug responses due to genetic factors. Early studies focused on pharmacokinetic aspects of drug response, but the advent of genomic perspectives added an emphasis on pharmacodynamic aspects as well.

In the pharmacokinetic realm, variations in the cytochrome P450 enzymes are

responsible for much of the variability in drug response. Rates at which drugs are metabolized vary up to 100-fold between normal and poor metabolizers. High drug levels over prolonged periods can exaggerate therapeutic effects or produce adverse side reactions. The CYP2D6 polymorphism, for example, causes poor metabolism of many common central nervous system drugs in up to 10% of Caucasians. The CYPC219 variant affects less than 5% of Caucasians, but 20% of Asians.

Rates at which drugs are metabolized may vary as much of 100-fold between normal and poor metabolizers. Such variations translate to variations in levels of a drug in the blood and in the duration of the drug's stay in the blood. High blood levels over a prolonged period can exaggerate the therapeutic effect or produce adverse side effects due, perhaps, to the enhanced production of toxic drug metabolites. The dangers of adverse drug effects in poor metabolizers are particularly evident with drugs having narrow therapeutic indices, such as cancer chemotherapeutic agents.

One lesson learned from these, and related, studies is that polymorphisms in single genes can significantly affect the action of common drugs. This situation stands in contrast to gene associations with complex diseases, for which multiple polymorphisms in several genes may have to act in concert. On the other hand, once a drug target is identified, variations only in that single gene may prove key to qualifying individuals for prescription of the corresponding drug. In the pharmacokinetic realm, multiple simultaneous biochemical pathways often play a role in the metabolism of a given drug, so that variations in several genes may have to be considered in deciding whether a drug candidate is likely to cause drug response problems.

Pharmaceutical companies have only recently started to test individuals slated for clinical trials for polymorphisms in relevant enzymes. The possibility of eliminating poor responders from the study population, or adjusting their dosages accordingly, provides pharmaceutical companies the opportunity to improve labeling for such drugs. Once the drug is on the market, the availability of a test to predict response can enhance the drug's market potential by improving both safety and efficacy for individuals.

Pharmacodynamic Considerations

The effects of genetic variation on the interaction of drugs with their targets constitute the pharmacodynamic dimension of pharmacogenomics. One of the earliest, and still one of the most exciting discoveries in this field involves the ApoE4 variant of the gene for apolipoprotein E (ApoE) and its relationship to Alzheimer's disease. Two drugs have so far been approved for the treatment of Alzheimer's. These are tacrine (Cognex®, Parke-Davis) and donepezil (Aricept™, Eisai), both cholinesterase inhibitors thought to compensate for low levels of brain acetylcholine in Alzheimer's patients. About one-quarter of Alzheimer's patients benefit from tacrine, and about the same proportion experiences serious adverse reactions, including hepatotoxicity.

The ApoE gene product appears to regulate the transport of cholesterol and phospholipids into the brain in response to tissue damage. Individuals bearing the ApoE4 allele have a decreased capacity to repair brain damage compared with individuals bearing the ApoE2 or ApoE3 alleles. Genetic variations in the ApoE gene have been found to predict susceptibility to the disease, while also providing information relevant to the choice of therapy. Individuals who were homozygous (two identical copies) of the ApoE4 variant responded much more poorly to tacrine than individuals with other ApoE genotypes. Consequently, an ApoE4 test to qualify responders could prove to be highly useful. Such tests are already in widespread use in pharmaceutical companies developing Alzheimer's drugs. Other useful examples involve patient response to the Abbott asthma drug, ABT-761, versus variations in ALOX5 gene, and work in which the clinical course of long QT syndrome patients is predicted by variations in LQT loci.

Integration of Therapeutics and Diagnostics

Pharmacogenomics holds the promise of devising molecular diagnostic assays that provide valuable input to the therapeutic decision-making process. Assays can be envisioned for screening products from variant disease genes either in asymptomatic or symptomatic individuals, for testing patient genetic variations relating to drug response, and testing genetic variations in viruses or other pathogens found in blood to determine their susceptibility to particular drugs.

Tests for drug response are particularly relevant when therapy is either expensive or risky and a substantial probability of non-response exists. Interferon-alpha and Herceptin™ are examples of expensive drugs with substantial non-responder populations. Chemotherapy for acute lymphoblastic leukemia with azathipurine or mercaptopurine provides an example in the risk category. Examples exist in each of the above categories. Tests are currently available for some of these, and others are in development.

1.2 Key Technologies and Applications

Pharmacogenomics is an experimental science, and whether one is dealing with its pharmacokinetic or pharmacodynamic aspects, measurements of genetic variation form its core. Polymorphisms play key roles as markers in the hunt for disease genes, drug target genes, and drug metabolism genes. When polymorphisms occur within disease genes themselves, they may signal the production of defective gene products. In either case, discovery and detection of such polymorphisms represent the essence of pharmacogenomics.

Key end goals of pharmacogenomics are 1) to identify and devise tests for genes determining drug response from both pharmacokinetic and pharmacodynamic perspectives and 2) to identify gene targets for complex diseases. In pursuit of these goals, three kinds of experiments, done in sequence, are useful. In the discovery phase, relatively few subjects are tested for many (1,000 or more) SNPs to identify candidate markers. In a second phase, a larger number (on the order of 100) subjects are tested for the candidate SNPs to determine their frequency in the population. Finally, a still larger number of cases and controls (on the order of 1,000) are studied for very few SNPs to pin down the marker-disease association. Glaxo Wellcome and the Whitehead Functional Genomics Consortium have performed studies in two or more of these categories. While high-density oligonucleotide microarrays have been useful for genome-wide studies, other methods are perhaps more appropriate for later stage investigations.

Classical methods for SNP detection, which are useful for small-scale investigations, emphasize manual operation and tend to rely on art. Most are based on fragment analysis. SSCP (single-strand conformational polymorphism) and updated variants are the most common of these. Heteroduplex analysis involves differences in melting temperatures between perfectly matched and single-mismatch hybrids. Allele-specific oligonucleotide (ASO) hybridizations, which form the basis for microarray methods, rely on stringent washing conditions to eliminate mismatched labeled target fragments from immobilized probes, leaving behind label corresponding only to perfect matches. Oligonucleotide ligation assays are similar to ASO methods, but add specificity based on enzymatic ligation of perfect-match probe pairs.

Early methods based on these principles lack the robustness required for industrial-strength genotyping. A number of manufacturers have deployed updated systems and others are in development. In the category of cleavage-based methods, Perkin-Elmer's (PE's) TaqMan® assay, in which a fluorescent tag is liberated from a quenching environment when a particular SNP is present, is on the market and has been used in several major genotyping studies. Third Wave Technologies is currently deploying its Invader™ assay for SNPs, in which the presence of a SNP results in cyclical cleavage of labeled oligos. The method is distinguished by the lack of a required separate PCR amplification step. Variagenics uses a resolvase enzyme to recognize and remove mismatched sequences.

Ligation-based methods include PE's HyChip™ assay licensed from HySeq, which ligates perfect-match labeled oligos to a universal microarray, and the ZipCode™/OLA assay, in which labeled perfect-match probes are ligated to address oligos for ultimate capture on a complementary address microarray. Amersham Pharmacia Biotech (AP Biotech) is developing ligation-based RCA (rolling circle ampli-fication) technology for SNP-detection, which permits very rapid amplification.

Primer extension-based SNP detection methods, which are quite popular for their relative simplicity and high throughput, involve annealing primers to targets and determining the nature of a SNP by extension with mixtures containing dideoxynucleotide chain terminators. The Sequenom method produces varying length primers depending on the presence or absence of a SNP. Lengths are measured by mass spectrometry. Orchid Biocomputer is deploying a robotics-automated version of its GBA® method, which uses enzyme-antibody conjugates to determine which terminator was added. Pyrosequencing relies on enzymatic method that generates light when a base has been successfully

incorporated into a primer.

ASO-based methods are best exemplified by Affymetrix's high density (300,000 or more oligos per chip) GeneChip® approach to genome-wide SNP detection. These devices, made by a proprietary light-protected parallel synthetic method, use four oligos, differing only by one central base, for each SNP to be detected. Protogene offers much lower density chips made by a conventional synthetic scheme implemented with ink-jet printers. These devices appear more readily applicable to custom microarray production. The aforemen-tioned HyChip and ZipCode/OLA methods belong in this category as well. Illumina is developing virtual microarray technology in which oligos are held on encoded beads, which are captured after hybridization to labeled targets on fiber-optic bundles. Yet another method in this category comes from Rapigene and involves mass spectral detection of ASOs labeled with cleavable small organic molecule tags with side chains that vary in molecular mass.

Heteroduplex-based methods have been modernized by several companies. Transgenomic has deployed a temperature-modulated heteroduplex analysis system based on detection of mismatched hybrids by HPLC. Varian Instruments has adapted one of its standard HPLC systems for the same sort of approach to SNP analysis. Hybaid, a division of Thermo BioAnalysis, uses an intercalated fluorescent dye to measure the melting temperatures of hybrids. Finally, Gene Check's system uses an immobilized mismatch binding protein to sequester mismatched sequences.

For genome-wide SNP scanning, Affymetrix has the only viable system that is currently on the market. Illumina's system, when completed, would appear to be broadly scalable for scanning many or few SNPs per specimen. Pricing remains an issue, since Affymetrix is targeting $0.10 per SNP for the future, while the market appears to want prices in the range of $0.01 per SNP. Other suppliers face similar pricing issues.

For detecting medium to low numbers of SNPs per specimen, primer extension approaches appear to be the most popular among manufacturers, particularly because they are amenable to high-speed detection methods, including mass spectrometry. Third Wave's Invader™ assay must be considered a force to contend with, based on its single-step protocol, which avoids separate PCR. A microfluidics-based electrophoresis approach, under development at Kiva Genetics, may also prove highly attractive because of its low reagent volume requirements and high speed. PE's TaqMan® assay, while currently considered expensive, is undergoing substantial miniaturization and multiplexing, and must be considered a commercial contender as well.

1.3 Market Analysis

Economic Issues

Pharmacogenomics can supply improved medical outcomes with fewer adverse drug reactions and less time and money spent on ineffective therapies. Yet achieving these goals will require that the healthcare system pay for expensive diagnostic procedures and individualized drugs before their value has been fully established. It may therefore be incumbent on the industry to demonstrate the cost-benefit advantages of these new modalities.

Big pharma's interest in pharmacogenomics stems from both the possibility of finding vastly improved targets for the developments of drugs against high-market potential diseases and the possibility of developing a new class of high-value-added drugs based on patient stratification. There exists also the highly attractive prospect of using pharmacogenomics to eliminate compounds early in the discovery/ development cycle and to reduce the costs and improve the quality of clinical trials through the rational selection of subjects.

Regulatory Impacts

The FDA is taking a largely reactive position in response to pharmacogenomics, reflecting the largely hypothetical current state of the field. The agency has, however, issued two guidances that discuss the importance of genetic polymorphisms in studying the metabolism of drug candidates. The context of these discussions places pharmacogenetic studies as one of several important modalities for studying metabolism. One of these documents states, "When a genetic polymorphism affects an important metabolic route of elimination, large dosing adjustments may be necessary to achieve the safe and effective use of the

drug."

A noteworthy aspect of pharmacogenomic data relates to differences among races and ethnic groups with respect to polymorphisms that can affect the safety and efficacy of drugs. If pharmaceutical companies were able to produce data relevant to ethnicity in the original clinical trials, then they might be able to avoid repeating such studies in seeking foreign approvals.

Aside from the FDA and the drug approval perspective, there are considerable concerns in public circles regarding the current and future implications of genetic testing. Existing genetic tests are primarily "home-brewed" in medical laboratories rather than taken from kits that have been approved by the FDA. Congress has heard testimony from experts in the field calling for greater regulation of such tests to assure safety and efficacy. Regulation may also extend to the pre- and post-analytical aspects of such testing (e.g., with respect to counseling of patients).

Impacts on the Healthcare Enterprise

Not only will pharmacogenomics have major impacts on healthcare systems, but the economics of healthcare delivery may have negative impacts on pharmaceutical innovation in general and pharmacogenomic products and perspectives in particular. From a more positive perspective, pharmacogenomics can save patients a great deal of suffering from adverse drug reactions and delayed attainment of therapeutic efficacy, just as it can save healthcare reimbursers the very substantial costs associated with these problems.

Developed nations face upward-spiraling medical costs, due in large measure to technological innovation, demographic shifts, and increases in life expectancy. Although the U.S. remains relatively free of drug price controls, this condition is not necessarily permanent. Price controls and other reimbursement limitations would have negative impact on investment in new technology.

However, the potential impacts of pharmacogenomics on healthcare delivery are overwhelmingly positive. Assuming that major diseases can be genetically subdivided and that batteries of drugs targeted to subgroups can be developed and cover most individuals (major assumptions, admittedly), then medicine will have made a quantum leap in the direction of better outcomes, greater medical efficiency, and reduced healthcare costs.

Pharmacogenomics has much to offer to a managed-care, health-maintenance environment that wants cost-effective therapies, disease management programs, improved drug efficacy, and better drug safety. The application of combined diagnostic tests and stratifiable drugs promises to address these concerns and to reduce the number of physician visits required to achieve satisfactory outcomes. Potentially, the greatest possible benefits to the worldwide healthcare delivery system will come from a major paradigm shift in which views on the nature of disease and the means to treat it undergo revolutionary changes.

Impacts on Society

Key issues facing healthcare in the early decades of the new millennium will be the extent to which privacy of information can be maintained, the extent to which such information is misused by third party payers, and the extent to which lawmakers will permit the gathering and dissemination of such information. With the ability to detect disease susceptibility genes, a significant portion of the population could end up in danger of insurance, employment, or other form of discrimination should key information not be properly protected. Yet because of the important ramifications of such information, it may prove difficult for society to afford the necessary protections. The use of genetic information in guiding procreation opens another set of difficult questions. Legislators have begun the onerous task of sorting through the complex issues and ramifications of such considerations. The experience of deCODE in gaining exclusive access to public database records in Iceland provides a foretaste of experiences to come in the rest of the developed world.

Social issues are colored by the negative implications of eugenics and its association with the Second World War. Eugenics has been making something of a comeback in the context of cloning and gene replacement technologies. Eugenics fears are exacerbated by findings that certain genetically isolated ethnic groups may be susceptible to particular genetic diseases. A number of genes have been identified recently that are believed to have an impact on human behavioral traits.

The possible identification of behavior with race or ethnicity is at best uncomfortable, and at worst, incendiary.

Issues surrounding the issuance of patents for genes and markers provide another source of social controversy relevant to pharmacogenomics. A recent news release indicates that the U.S. and U.K. are working on an agreement that would prevent the patenting of genes by private companies and assure that newly discovered genes are disclosed to the public in a timely manner. Formation of the SNP Consortium by the Wellcome Trust and ten major pharmaceutical companies indicates overlap in the interests of public sector and academic scientists with businesses seeking to avoid the high costs associated with licensing such discoveries from smaller companies.

Pharmacogenomic Business Strategies

No major pharmaceutical company can afford to ignore pharmacogenomics completely, and it appears highly unlikely that any are in fact doing so. Many are, however, cautiously dipping toes in the water, while others have plunged in with, if not wild abandon, then a sense of keen interest and research investment to match. Pharmacogenomic strategies vary depending on a company's current business structure and strategic thrust.

Abbott Laboratories and Hoffmann-LaRoche, for example, both have very substantial positions in diagnostics, and their efforts to link therapeutics with diagnostics are colored by interest in building value for that end of the business and finding synergies between pharmaceuticals and diagnostics. Roche, which has been the more active of the two, is involved in substantial collaborations with deCODE and CuraGen. Glaxo Wellcome, arguably the pharmacogenomics leader in big pharma, is active both internally via its BINgenetics program and Clinical Genetics Network, and externally through a substantial collaboration with CuraGen. Other companies vary in their commitment to pharmacogenomics.

For purposes of this analysis, small companies have been divided into three categories – tool providers, genomics companies, and pharmacogenomics companies. Tool providers are those companies that have a significant proprietary technology relevant to pharmacogenomic analysis. Genomics companies are those whose main thrust is the discovery of genes by non-pharmacogenomic approaches, but which have a pharmacogenomic component to their operations. Pharmacogenomics companies are primarily those that emphasize either the gathering of phenotypic and genotypic information into databases or that provide pharmacogenomic analytical services to larger companies.

Among tool providers, Affymetrix stresses genome-wide screening applications because its technology is best suited to high-density microarrays. An upcoming competitor, Illumina, may develop the capacity to cover both the many-SNP and few-SNP per sample ends of the market by virtue of its scalable "virtual microarray" technology. Third Wave's Invader™ technology provides protocol simplicity at the cost of some chemical complexity. A combination of the Third Wave technology with the Illumina detection system, rumored to be under consideration, could be a very powerful commercial contender. Orchid Biocomputer, which is already selling SNP detection kits, is making a multi-faceted effort to establish itself as a leader in SNP detection, while Sequenom is working to establish a similar identity as the industrial-strength sequencing alternative. Perkin-Elmer, already a force to contend with based on the TaqMan product, has a broad array of upcoming alternative genotyping technologies and appears to be taking something of a shotgun approach to the market.

Genomics companies are primarily sellers of information and intellectual property, relying on large pharmaceutical and biotechnology companies for deals with both front and back-end consequences. Approaches to pharmacogenomics vary. Millennium has sequestered all these activities in a diagnostics-oriented subsidiary, Millennium Predictive Medicine. Incyte, which has formed a genetics subsidiary centralizing SNP-mapping and proteomics activities, is also involved in a diagnostics joint venture with SmithKline Beecham called diaDexus. Genset has made its 60,000-SNP map the center of a broad array of pharmacogenomics deals, including a pioneering arrangement with Abbott. Celera, the youngest of the major genomics companies, plans to uncover more than 1 million SNPs in the course of its accelerated genome sequencing effort and to develop the definitive SNP map. Perkin-Elmer is using Celera as a key element in its strategy to move up the value chain. Genomics companies tend to view genetic variation data as one element in a broader array of perspectives and technologies that provide information to their clients. Competition comes both from pharmacogenomics boutiques and from

internal programs in big pharma.

Pharmacogenomics companies, including deCODE, Eurona, Gemini, Genaissance, and Oxagen, are establishing extensive databases of genotypes to match patient's phenotypic medical information. The goal is to identify disease genes leading to new drug targets. Each company in this category seeks partnerships with major pharmaceutical and biotechnology companies. Other companies in this category, including Algene, Rapigene, Variagenics, and Axys, offer pharmacogenomic services to corporate customers. Strategies vary within these broader subcategories. Several companies have proprietary genotyping technologies, while others have diagnostic aspirations.

Pharmacogenomic Deals

A broad diversity of deal types exist in pharmacogenomics. A majority of deals between pharmaceutical companies and genomics companies center on the discovery of disease genes and drug targets through studies of genetic variation. Other deals between smaller companies tend to involve functional synergies. Examples include the Celera-Gemini arrangement and the Incyte-Oxford Glycosciences proteomic database deal. Genotype-phenotype database companies have yet had little success in generating substantial collaborations. The deCODE-Roche collaboration is the most extensive in this category. More activity is expected as the databases grow in scope and value, but interim funding remains a key issue.

Another category of deals involves the acquisition of genotyping technologies. AP Biotech's licensing of Rolling Circle Amplification from Molecular Staging is an example of this genre, as is Incyte's acquisition of Hexagen. Two deals have resulted in establishing pharmacogenomic service providers. One involves Axys and PPD, while the other involves Variagenics and Quintiles.

The Competitive Environment

Competition for markers derived from pharmacogenomics focuses on relatively few disease areas. Four categories – psychiatric/neurologic, cancer, osteoporosis, and cardiovascular – dominate the competitive picture. A second tier of emphasis falls on asthma, hypertension, obesity, and diabetes. In each of these genetically complex disease areas, the size of the market opportunity justifies the search for markers that will lead to drug targets applicable to subsets of individuals with genetically distinct sub-classes of disease. While the actual research emphases of pharmaceutical companies will differ in detail, clearly there is considerable overlap in disease emphasis. In some sense, competition is perhaps too strong a word to describe big pharma's involvement in pharmacogenomics. In fact, the very existence of the SNP Consortium is evidence that the subject is too large and complex for any one company to take on by itself.

Competition among tool providers heated up as 1999 progressed toward the millennium. As of September, there were relatively few genotyping systems actually on the market, but several impressive products were on the verge of introduction. Affymetrix has an early lead in genome-wide scanning, while a large number of contenders are positioning themselves in the downstream market involving few SNPs per sample. Leading contenders include Perkin-Elmer, Third Wave Technologies, Orchid, Sequenom, and Illumina.

Revenue Impacts of Pharmacogenomics

Specific analysis of the net effects of pharmacogenomic activities on the revenue and profit pictures of either the pharmaceutical industry or individual companies is premature considering that programs are still in their very early stages. No company has yet made an irreversible commitment to the implementation of patient stratification for either clinical studies or drug prescription. Comments by industry leaders suggest that Pandora's box has been opened, and that some microsegmentation of markets will be an inevitable result of patient stratification.

Broad acceptance of pharmacogenomics would appear to require adherence to at least two conditions. First, business models that are revised in light of pharmacogenomics must permit annual double-digit increases in overall revenues and profits for participating companies. Second, drug development programs must offer significantly improved returns on investment. It will not serve the industry to reduce R&D costs if these savings are more than offset by reduced market potential due to elimination of non-responders or those predicted to suffer adverse reactions.

The main benefits of pharmacogenomics may be less involved in directly improving a company's competitive position than in enhancing the value of drugs and, therefore, their price. If improvements in efficacy (and safety as well) from pharmacogenomics are sufficiently large in terms of improved medical outcomes, revenue increases should greatly exceed any losses of market share from elimination of non-responders. A significant pharmacogenomics contribution to medical outcomes is expected to add on the order of $500 million per year in extra revenue for each drug.

Regarding pharmagenomic tool and service providers, projections indicate revenues for 2000 totaling more than $140 million and growing by 2006 to just over $1 billion. Service providers dominate the revenue picture for 2003, but the two segments return to rough equivalence by 2006. From an applications perspective for tool providers, genome-wide scans and gene-disease association studies dominate the revenue picture during 2000. The diagnostic sector becomes a significant factor by 2003 and, along with association studies, dominates the revenue picture by 2006. A further breakdown indicates that consumables (versus instruments and software) account for 70% of the tool provider revenue total for 2000, but for 90% of the total by 2006.

Future Trends

Two pharmaceutical revolutions are possible as a result of accelerated technological development and the results of pharmacogenomic studies. One involves the way drugs are developed, the other involves the way drugs are administered. Drug response genetics appears likely to prove its value in drug development. Improvements in this category appear evolutionary rather than revolutionary. The use of genetic variation in the search for new genes relevant to the elusive complex, high-incidence diseases has the potential for a real pharmaceutical-medical revolution. It must be noted, however, that the common-disease-common variant hypothesis described this report is, at this point, simply a theoretical formulation that is still awaiting proof-of-concept.

Strong suspicions exist that a Mother Lode of pharmacologically valuable information is waiting to be harvested, but the amount of such information and the extent of its value remain to be determined. The search is fueled by a few intriguing examples, none of which has yet provided a pharmaceutical breakthrough. Of course, the massive studies needed to test the hypothesis provide a lesser revolution for the bioanalytical start-ups and established companies that are inventing and developing the relevant and highly sophisticated technologies.

On the drug administration front, the individualization of drug therapy promises what could easily be a major revolution not only in drug prescription, but also in healthcare delivery in general. Drugs today save many lives and improve the quality of life for many millions of individuals. Yet the benefits of drug therapies come at a price. Almost every drug on the market is relatively ineffective for a significant proportion of the patients receiving it, and, worse, many drugs cause serious adverse reactions in non-trivial percentages of patients to which they are administered. Of course, the existence of a subpopulation of individuals with a particular disease, having a genetic variation that might lead to the development of a new drug, does not mean that it will be economically feasible to undertake such a project.

A likely scenario sees pharmacogenomics significantly impacting drug development after about five years, having a major impact on drug discovery after about seven years, and delivering individualized therapy after about twelve years. Impacts in each of these areas should be felt sooner than these target times. However awaiting the maturation of pharmacogenomics will require some patience and fortitude.

Who Will Be the Big Winners

The pharmaceutical industry as a whole stands to win big or lose big depending on whether or not pharmacogenomics succeeds in delivering abundant and improved targets for complex diseases and in achieving patient stratification for improved hypothesis-based medicine. Pharma's "innovation deficit" stems, arguably, from a drug discovery paradigm that is running out of steam. Pharmaceutical research still has a long way to go before it truly deserves to be considered scientific with regard to predictability. The notion that the tools of modern genomics coupled with effective research IT tools may provide answers to some key fundamental

questions is compelling to an industry that desperately needs new ways to improve productivity and, perhaps more importantly, to add significant value to its new product offerings.

Perhaps even more important is the notion that pharmacogenomics could act as a springboard for changing the nature of the pharmaceutical business so that companies are no longer simply makers and sellers of drugs, but purveyors of improved patient outcomes with major benefits to themselves, patients, and healthcare delivery economics on a broad scale.

Biotechnology companies that provide the tools for pharmacogenomics research have much to gain in short-term revenues as pharmaceutical and biotechnology drug researchers sort through a variety of approaches to genotyping. Those that pass the test of both technical and cost-effectiveness have even more to gain from the large number of massive experiments to be performed in coming years. No doubt some, perhaps a majority, of tool providers will fall by the wayside as others have their technologies and products broadly accepted. It may also be reasonable to assume that winners in the many patient-few SNPs segment of testing are pre-qualified to become winners in the ultimate new-paradigm diagnostics industry, which will provide the tests needed to fit the "right drug to the right patient at the right time."

The individual patient could become the ultimate beneficiary of a revamped healthcare delivery paradigm based on better drugs and better prescribing through pharmacogenomics. There are, however, problems that stand in the way of realizing the dream. For example, some genetic variations that signal a favorable response may also indicate susceptibility to disease. Testing individuals for such genetic variations may brand them as poor risks for health insurance. Such stigmatization could result in losing jobs or not being hired in the first place. A protracted and complex process of sorting out privacy issues awaits the industry.

Of course, the simple notion of developing a drug for a group of individuals that can be qualified based on a test ignores some broader issues in healthcare delivery. Lacking the sophisticated operational policies and control mechanisms of some of the more successful HMOs, corporations with relatively poorly managed clusters of physician group practices have difficulty to varying degrees in maintaining control of the quality of healthcare provision. The best of technological innovations in medicine is no better than physicians' ability to administer it.

It would appear, however, that the trend toward centralization and integration in healthcare delivery will continue unabated despite public concerns to the contrary. Kaiser Permanente, a large HMO with a good mixture of business and medical perspectives in its administration, is currently one of the more economically viable managed care organizations in the U.S., and may well provide a model for the future of healthcare delivery. The integration and standardization of care fits nicely with the pharmacogenomic perspective.

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